

SEQUENCE LISTING

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<110> Amylin Pharmaceuticals, Inc.
       Baron, Alain et al.
<120> COMPOSITIONS FOR THE TREATMENT AND PREVENTION OF NEPHROPATHY
<130> 18528.675 (0218-UTL-9)
<140> 10/741,534
<141> 2003-12-19
<150> 10/740,146
<151> 2003-12-17
<150> 60/434,508
<151> 2002-12-17
<150> 60/434,888
<151> 2002-12-19
<160> 34
<170> PatentIn Ver. 3.2 and Microsoft Word
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      AMIDATION, Arg at position 30 may optionally be Amidated
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His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg
            20
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<223> artificial sequence with specific variable residues

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       4-imidazopropionyl (des-amino-histidyl), 4-imidazoacetyl, or
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       4-imidazo-alpha, alpha dimethyl-acetyl
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      variant
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      (20)..(20)
      Lys or Arg
<223>
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      variant
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      (28)..(28)
<223> Lys at position 28 is optionally branched with a C6-C10 unbranched acyl
       group
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<223> Gly-OH or NH2
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Xaa Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly
                5
                                    10
                                                         15
Gln Ala Ala Xaa Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Xaa
                                25
                                                     30
            20
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<220>
      variant
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<223> X at position 1 is NH2, NH2-Ser, NH2-Val-Ser or NH2-Asp-Val-Ser
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      variant
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       (18)..(18)
<223>
      X at position 18 is Lys or Arg
<220>
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<222>
      (21)..(21)
<223> X at position 21 is NH2, OH, Gly-NH2, or Gly-OH
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<400> 3
Xaa Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu
                                    10
Val Xaa Gly Arg Xaa
            20
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      NH2-Ser-Asp-Val-Ser
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<221>
      variant
<222> (18)..(18)
<223> X at position 18 is Lys or Arg
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<221>
      variant
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      (21)..(21)
<223> X at position 21 is NH2, OH, Gly-NH2, or Gly-OH
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Xaa Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu
                                    10
                                                        15
Val Xaa Gly Arg Xaa
            20
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<223> X at position 18 is Lys or Arg
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<223> X at position 21 is NH2, OH, Gly-NH2, or Gly-OH
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Val Xaa Gly Arg Xaa
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                5
                                    10
                                                        15
Val Xaa Gly Arg Xaa
            20
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<223> X at position 1 is Lys or Arg
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Val Xaa Gly Arg Xaa
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<223> X at position 18 is Lys or Arg
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<222> (21)..(21)
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Val Xaa Gly Arg Xaa
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<223> X at position 18 is Lys or Arg
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<223> X at position 21 is NH2, OH, Gly-NH2 or Gly-OH
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Val Xaa Gly Arg Xaa
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<223> X at position 18 is Lys or Arg
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<223> X at position 21 is NH2, OH, Gly-NH2 or Gly-OH
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Val Xaa Gly Arg Xaa
            20
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      (29)..(29)
\langle 223 \rangle X at position 29, if GLP-1 (7-35) is Gly
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<223> X at position 29, if GLP-1 (7-36) is Gly-Arg
<220>
<221> variant
<222> (31)..(31)
<223> X at position 29, if GLP-1 (7-37) is Gly-Arg-Gly
<400> 11
His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Xaa Xaa Xaa
                                25
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<213> Heloderma horridum
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<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2
<400> 12
His Ser Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
                                     10
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
Ser Gly Ala Pro Pro Pro Ser
         35
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<223> AMIDATION
<400> 13
Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu
Trp Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser
            20
                                25
<210> 14
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<213> Heloderma suspectum
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<221> MOD RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2
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<400> 14

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu  $1 \hspace{1cm} 5 \hspace{1cm} 10 \hspace{1cm} 15$ 

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser 20 25 30

Ser Gly Ala Pro Pro Pro Ser

<210> 15

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<400> 15

His Ser Asp Ala Thr Phe Thr Ala Glu Tyr Ser Lys Leu Leu Ala Lys
1 10 15

Leu Ala Leu Gln Lys Tyr Leu Glu Ser Ile Leu Gly Ser Ser Thr Ser 20 25 30

Pro Arg Pro Pro Ser Ser 35

<210> 16

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<400> 16

Leu Ala Leu Gl<br/>n Lys Tyr Leu Glu Ser Ile Leu Gly Ser Ser Th<br/>r Ser 20  $\phantom{000}25\phantom{000}$ 30

Pro Arg Pro Pro Ser 35

<210> 17

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His Ser Asp Ala Ile Phe Thr Glu Glu Tyr Ser Lys Leu Leu Ala Lys
Leu Ala Leu Gln Lys Tyr Leu Ala Ser Ile Leu Gly Ser Arg Thr Ser
            20
                                25
Pro Pro Pro
        35
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                5
Leu Ala Leu Gln Lys Tyr Leu Ala Ser Ile Leu Gly Ser Arg Thr Ser
            20
                                25
                                                    30
Pro Pro Pro
        35
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<223> Exendin-4 (1-30)
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His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
               5
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly
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                25
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                                  10
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly
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                                    10
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
            20
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<223> 14-Leu, 25-Phe form of exendin-4
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<222> (39)..(39)
<223> Ser-NH2
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Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser
                                25
Ser Gly Ala Pro Pro Pro Ser
        35
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<223> Truncated form of 14-leu, 25-Phe exendin-4
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His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu

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5
Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20
                               25
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<223> 14-Leu, 22-Ala, 25-Phe form of exendin-4(1-28)
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<223> Asn-NH2
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His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
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Glu Ala Val Arg Leu Ala Ile Glu Phe Leu Lys Asn
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1

15

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       indicated in the specification
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                                               15
                              10
25
          20
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<222> (5)..(5)
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      (8)..(8)
<223> Ala, Ser or Thr
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      (9)..(9)
<223> Ala, Asp or Glu
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      (10)..(10)
<223> Ala, Leu or pentylglycine
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<223> Ala or Ser
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<223> Ala or Lys
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<222> (19)..(19)
<223> Ala or Val
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     (22)..(22)
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     (23)..(23)
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      (25)..(25)
<223> Ala, Trp or Phe
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     (26)..(26)
<223> Ala or Leu
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     (27)..(27)
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     VARIANT
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     (28)..(28)
<223> Ala or Asn
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      (29)..(29)
     -OH, -NH2, Gly-OH, Gly-NH2, Gly Gly-ON, Gly Gly-NH2 and further
      as indicated in the specification
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<223> Formula VII: Artificial sequence with specific variable residues
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      (1)..(1)
<223> His, Arg, Tyr or 4-imidazopropionyl
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      (2)..(2)
<223> Ser, Gly, Ala or Thr
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<222> (3)..(3)
<223> Asp or Glu
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      (5)..(5)
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      VARIANT
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      (6)..(6)
<223>
      Ala, Phe, Tyr or naphthylalanine
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      (7)..(7)
<223> Thr or Ser
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      VARIANT
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<223> Ala, Ser or Thr
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<222> (9)..(9)
<223> Asp or Glu
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Xaa Ala Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa

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      (10)..(10)
<223> Ala, Leu, Ile, Val, pentylglycine or Met
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      VARIANT
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      (11)..(11)
<223> Ala or Ser
<220>
<221> VARIANT
<222>
      (12)..(12)
<223> Ala or Lys
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      VARIANT
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      (13)..(13)
<223> Ala or Gln
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      VARIANT
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      (14)..(14)
<223> Ala, Leu, Ile, pentylglycine, Val or Met
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<221>
      VARIANT
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      (15)..(17)
<223> Ala or Glu
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      (19)..(19)
<223> Ala or Val
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      (20)..(20)
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      (21)..(21)
<223> Ala, Leu or Lys-NH.Sigma.-R, where R is Lys, Arg, C1-C10 straight-chain
       or branched alkanoyl or cycloalkanoyl
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      VARIANT
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      (22)..(22)
<223>
      Phe, Tyr or naphthylalanine
<220>
<221>
      VARIANT
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      (23)..(23)
<223>
      Ile, Val, Leu, pentylglycine, tert-butylglycine or Met
<220>
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<223> Ala, Glu or Asp
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      VARIANT
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<223> Ala, Trp, Phe, Tyr or naphthylalanine
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<221> VARIANT
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     (26)..(26)
<223> Ala or Leu
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<221>
     VARIANT
<222> (27)..(27)
<223> Lys Asn, Asn Lys, Lys-NH.Sigma.-R Asn, Asn Lys-NH.Sigma.-R, Lys-
     NH.Sigma.-R Ala, Ala Lys-NH.Sigma.-R where R is Lys, Arg, C1-C10
     straight-chain or branched alkanoyl or cycloalkylalkanoyl
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      30
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      4imidazopropionyl
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      (2)..(2)
<223> Ser, Gly, Ala or Thr
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      Ala, Asp or Glu
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      (4)..(4)
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      Ala, Norvaline, Val, Norleucine or Gly
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      VARIANT
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      (5)..(5)
      Ala or Thr
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      VARIANT
<222>
      (6)..(6)
      Phe, Tyr or naphthylalanine
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<220>
<221>
      VARIANT
<222>
      (7)..(7)
<223>
      Thr or Ser
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<221>
      VARIANT
<222>
      (8)..(8)
<223>
      Ala, Ser or Thr
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      VARIANT
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       (9)..(9)
       Ala, Noraline, Val, Norleucine, Asp or Glu
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      VARIANT
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      (10)..(10)
<223>
      Ala, Leu, Ile, Val, pentylglycine or Met
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      VARIANT
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      (11)..(11)
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      Ala or Ser
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      VARIANT
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       (12)..(12)
<223>
      Ala or Lys
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      VARIANT
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      (13)..(13)
<223> Ala or Gln
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       (14)..(14)
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<221>
      VARIANT
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      (15)..(17)
<223> Ala or Glu
<220>
<221>
      VARIANT
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      (19)..(19)
<223> Ala or Val
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<221>
      VARIANT
<222>
      (20)..(20)
<223> Ala or Arg
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.<221>
      VARIANT
<222>
       (21)..(21)
<223> Ala, Leu or Lys-NH.Sigma.-R where R is Lys, Arg, C1-10 straight-chain
       or branched alkanoyl or cycloalleyl-alkanoyl
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<221>
      VARIANT
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       (22)..(22)
<223>
      Phe, Tyr or naphthylalanine
<220>
<221>
      VARIANT
<222>
       (23)..(23)
       Ile, Val, Leu, pentylglycine, tert-butylglycine or Met
<223>
<220>
<221>
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       (24)..(24)
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      Ala, Glu or Asp
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       (25)..(25)
<223>
      Ala, Trp, Phe, Tyr or naphthylalanine
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<221>
      VARIANT
<222>
       (26)..(26)
<223>
      Ala or Leu
<220>
<221>
       VARIANT
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       (27)..(27)
       Lys Asn, Asn Lys, Lys-NH.Sigma.-R Asn, Asn Lys-NH.Sigma.-R, Lys-
<223>
       NH.Sigma.-R Ala, Ala Lys-NH.Sigma.-R where R is Lys, Arg, C1-C10
```

## straight-chain or branched alkanoyl or cycloalkylalkanoyl

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     (28)..(28)
<223> -OH, -NH2, Gly-OH, Gly-NH2, Gly Gly-ON, Gly Gly-NH2 and further
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                           25
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     (2)..(2)
<223> Ser, Gly, Ala or Thr
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<222> (3)..(3)
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     VARIANT
<221>
<222>
     (6)..(6)
<223> Phe, Tyr or naphthylalanine
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<221>
     VARIANT
<222>
     (7)..(7)
<223>
     Thr or Ser
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<221>
     VARIANT
<222>
     (8)..(8)
<223> Thr or Ser
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      VARIANT
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      (9)..(9)
<223> Asp or Glu
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<221>
      VARIANT
<222>
      (10)..(10)
<223> Leu, Ile, Val, pentylglycine or Met
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      (14)..(14)
      Leu, Ile, pentylglycine, Val or Met
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      VARIANT
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      (22)..(22)
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      Phe, Tyr or naphthylalanine
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      (23)..(23)
      Ile, Val, Leu, pentylglycine, tert-butylglycine or Met
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      VARIANT
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      (24)..(24)
<223> Glu or Asp
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      (25)..(25)
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       Trp, Phe, Tyr or naphthylalanine
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      (31)..(31)
       Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine,
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       {\tt N-alkylpentylglycine}\ \ {\tt or}\ \ {\tt N-alkylalanine}
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      (36)..(38)
      Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine,
       N-alkylpentylglycine or N-alkylalanine
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      VARIANT
<222>
       (39)..(39)
       Ser-OH, Ser-NH2, Thr-OH, Thr-NH2, Tyr-OH or Tyr-NH2
<223>
<400> 31
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Xaa Xaa Xaa Gly Thr Xaa Xaa Xaa Xaa Ser Lys Gln Xaa Glu Glu

```
1
               5
                                                       15
Glu Ala Val Arg Leu Xaa Xaa Xaa Leu Lys Asn Gly Gly Xaa Ser
                                                    30
           20
                                25
Ser Gly Ala Xaa Xaa Xaa Xaa
        35
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<223> Formula X: artificial sequence with specific variable residues
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      VARIANT
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      (2)..(2)
<223> Ser, Gly, Ala or Thr
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<222> (6)..(6)
<223> Phe, Tyr or naphthylalanine
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      (7)..(7)
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      Thr or Ser
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      (8)..(8)
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      Ser or Thr
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      (9)..(9)
<223> Asp or Glu
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10

<220>

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<222> (14)..(14)
<223> Leu, Ile, pentylglycine, Val or Met
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<221> VARIANT
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      (22)..(22)
<223> Phe, Tyr or naphthylalanine
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      (23)..(23)
<223> Ile, Val, Leu, pentylglycine, tert-butylglycine or Met
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      (24)..(24)
<223> Glu or Asp
<220>
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      VARIANT
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      (25)..(25)
<223> Trp, Phe, Tyr or naphthylalanine
<220>
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<222> (27)..(27)
<223> Lys, Asn, Asn, Lys, Lys-NH.Sigma.-R Asn, Asn, Lys-NH.Sigma.-R where R is
       Lys, Arg, C1-C10 straight-chain or branched alkanoyl or
       cycloalkylalkanoyl
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<221> VARIANT
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      (30)..(30)
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<223>
       N-alkylpentylglcyine or N-alkylalanine
<220>
<221> VARIANT
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      (35)..(37)
<223> Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine,
       N-alkylpentylglcyine or N-alkylalanine
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<221>
      VARIANT
<222>
      (38)..(38)
<223> Ser-OH, Ser-NH2, Thr-OH, Thr-NH2, Tyr-OH or Tyr-NH2
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Xaa Xaa Xaa Ser Lys Gl<br/>n Xaa Glu $\cdot$  Glu

1 5 10 15

Glu Ala Val Arg Leu Xaa Xaa Xaa Leu Xaa Gly Gly Xaa Ser Ser 20 25 30

Gly Ala Xaa Xaa Xaa Xaa 35

<210> 33

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<212> PRT

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<220>

<223> Formula XI: artificial sequence with specific variable residues

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<223> X is His, D-His, desamino-His, 2-amino-His, beta.hydroxy-His, homo-His, alpha-fluoromethyl-His, or alpha-methyl-His

<220>

<221> VARIANT

<222> (2)..(2)

<223> X is Met, Asp, Lys, Thr, Leu, Asn, Gln, Phe, Val or Tyr

<220>

<221> VARIANT

<222> (15)..(15)

<223> X is Glu, Gln, Ala, Thr, Ser or Gly

<220>

<221> VARIANT

<222> (21)..(21)

<223> X is Glu, Gln, Ala, Thr, Ser or Gly

<220>

<221> VARIANT

<222> (31)..(31)

<223> X is NH2 or Gly-OH, provided that if X at position 1 is His, X at position 2 is Val, X at position 15 is Glu and X at position 21 is Glu, then X at position 31 is NH2

<400> 33

Xaa Xaa Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Xaa Gly  $1 \hspace{1cm} 5 \hspace{1cm} 10 \hspace{1cm} 15$ 

Gln Ala Ala Lys Xaa Phe Ile Ala Trp Leu Val Lys Gly Arg Xaa 20 25 30

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       31
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      PRT
<213>
      artificial sequence
<220>
<223> Formula XII: artificial sequence with specific varibale residues
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<221>
      variant
<222>
      (1)..(1)
<223> X is His, D-His, desamino-His, 2-amino-His, beta.hydroxy-His,
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<220>
<221>
      variant
<222>
      (2)..(2)
<223> X is Ala, Gly, Val, Thr, Ile, or alpha-methyl-Ala
<220>
<221>
      variant
<222>
      (15)..(15)
     X is Glu, Gln, Ala, Thr, Ser or Gly
<220>
<221>
      variant
<222>
      (21)..(21)
      X is Glu, Gln, Ala, Thr, Ser or Gly
<220>
<221>
      variant
<222> (31)..(31)
<223> X is
<220>
<221> variant
<222> (31)..(31)
<223> X is NH2 or Gly-OH, providing that the compound has an
       isoelectric point in the range from about 6.0 to about 9.0 and
       further providing that when X at position 1 is His, X at position
       2 is Ala, X at position 15 is Glu and X at position 21 is Glu, X
<400> 34
Xaa Xaa Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Xaa Gly
                                    10
                                                        15
Gln Ala Ala Lys Xaa Phe Ile Ala Trp Leu Val Lys Gly Arg Xaa
            20
                                25
```